PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Association of occupational dust exposure with combined chronic obstructive pulmonary disease and pneumoconiosis: a cross-sectional study in China
AUTHORS	Fan, Yali; Xu, Wenjing; Wang, Yuanying; Wang, Yiran; Yu, Shiwen; Ye, Qiao

VERSION 1 - REVIEW

REVIEWER	Satoshi Hamada Japan
REVIEW RETURNED	11-Apr-2020

GENERAL COMMENTS	1. Data of pulmonary function test are lacked. The authors should analyse data of pulmonary function test among patients with pneumoconiosis. 2. Discussion is too heavy.

REVIEWER	Kjell Torén Occupational and environmental medicine, Sahlgrenska University Hospital, Sweden
REVIEW RETURNED	04-May-2020

GENERAL COMMENTS	This is an interesting manuscript showing that we probably are overlooking the importance of COPD/CAL among patients with pneumoconiosis. However, to some extent the manuscript is confusing with results from methods not described in methods, but also there are some interesting results that not are presented. However, I think the manuscript has an important message. General comments: I am sceptic to use the overlap terminology, it reminds me about ACO, which is a condition that is on its way out. I would prefer to focus on the risk of COPD/CAL in relation to exposure to tobacco smoke and/or silica dust – both well known risk factors for these conditions. And probably overlooked among persons with pneumoconiosis. I am not convinced that the “overlap” condition is phenotype if itself, it is a matter of different exposure patterns. I would skip that part

	The definition of COPD is not clear. In the introduction is stated that COPD is CAL and symptoms (which I agree with), but later in the manuscript is the term “spirometry-defined COPD” introduced. What is that? Is it chronic airflow limitation, please be consistent regarding the used terms The lung function data is for me not totally clear. Here is a dynamic spirometry after bronchodilation, which is fine. But I lack which normal equations are used? I would also prefer to have the prevalence of CAL and restrictive spirometric pattern (RSP) in the different groups. TLC and RV are presented, but I cannot find that those are mentioned in the Methods. It would be of interest to get information about the prevalence of true restriction in these groups, based on the used normal values. The same with diffusion capacity. Even if they are from the hospital files, the clinical physiological laboratory have normal values and method descriptions. Bronchial challenge test is also mentioned??? Please, describe and specify. Specific comments Abstract In the abstract is COPD defined based on lung function. I think that is CAL. Introduction Is coal dust an inorganic dust?? I would start the introduction with the pneumoconiosis part, and the continue with CAL/COPD. It is the pneumoconiosis population that is the base of the study. Study procedure Reversibility of FEV1 is not airway hyperreactivity (at least not in my opinion) I think it is important to stress that emphysema and CAL are different conditions. You can have emphysema and “normal” lung function, at least not CAL. That has to be further discussed. In Table S1 the COPD group has FEV1/FVC ranging from 74 to 81.80. Does that mean that a pet9onet with COPD can have FEV1/FVC ratio =81.80. Please, explain that. Does it mean that the “COPD” group includes pat8ents with emphysema and normal lung function??. That is, however, not in accordance with the initial definitions in the manuscript. My final advices: Skip the overlap condition. Focus on the risk for CAL associated with exposure to tobacco smoke and silica dust among patients with pneumoconiosis Stress that we have overlooked this important aspect. Be careful with the details in the manuscript.

REVIEWER	Priya Paudyal Brighton and Sussex Medical School
REVIEW RETURNED	01-Jun-2020

GENERAL COMMENTS	The study is well conducted and the quality of the manuscript is very good. I just have few minor comments, mainly regarding the methodology. The results in the abstract could be presented in effect sizes rather than just saying the % increase. I am slightly confused with the study method. The method section says 'Patients with pneumoconiosis were consecutively recruited, from January 2016 to July 2019' and later says 'Clinical data were retrieved from medical records…' Did the study begin in 2016 with recruitment of participants or was it a retrospective database study based on medical records of the patients recruited between 2016-19, it needs some clarification. Also, if the sample size estimated was between 214-428, why the study included almost double number of participants? Why Mann Whitney test was used instead of T test? Was the distribution not normal? Also, in the multivariate analysis (Table 4), information should be provided on what variables were included in the model and whether the adjustments were made for these. The findings are well discussed.

REVIEWER	Christian Schyllert Umeå University, Department of Public Health and Clinical Medicine, Umeå, Sweden
REVIEW RETURNED	06-Jun-2020

GENERAL COMMENTS	This papers investigates the clinical features of COPD among patients with pneumoconiosis. It is a very interesting study with very important results, especially for clinicians in lung medicine. I have some comments below. 2) Is the abstract accurate, balanced and complete? I think the results section of the abstract can be condensed even more. For example maybe the first sentence could be in methods, to balance the sections up a little. I think the results could start with the sentence Patients with overlapping... that starts on row 31, or at least with the sentence COPD prevalence.. starting on roe 28. 3. Is the study design appropriate to answer the research question? I believe that describing the prevalence of COPD/pneumoconiosis makes one think of a study of the general population. Maybe in the introductions last paragraph clarify that it is a population of pneumoconiosis patients. Likewise I believe that saying you want to identify risk factors of overlap also needs to be clarified that it is overlap of COPD/pneumoconiosis among pneumoconiosis patients.

REVIEWER	Georgios Rachiotis University of Thessaly, Greece
REVIEW RETURNED	07-Jun-2020

GENERAL COMMENTS	I read with interest this well written paper which presented the results of a cross-sectional study on the prevalence and risk factors related to co-existence of pneumonoconiosis and COPD among Chinese industrial workers. Major points. 1. In the statistical analysis /methods section the authors stated that Mann Whitney test was used for the univariate analysis of continuous variables. Did the authors checked the data for normality? 2.I missed a statement in statistical analysis/methods section regarding the methdology used for the assessment of the possible interaction between smoking and work-related chemical hazards. 3. In the last sentence of the manuscript the authors concluded that they found:"high risk of occupational dust exposure for COPD and pneumoconiosis overlap and calls for urgent preventive intervention". They may further discuss this issue and they could mention examples of "urgent prteventive intervemtions" (e.g. combined control of smoking and occupational exposures).

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Satoshi Hamada

Institution and Country: Japan

Please state any competing interests or state ‘None declared’: None

Please leave your comments for the authors below

1. Data of pulmonary function test are lacked. The authors should analyse data of pulmonary function test among patients with pneumoconiosis.

Answer: We thank the reviewer’s comments. Data of pulmonary function test among the patients with pneumoconiosis were shown in the Supplementary Material (Table S1). The data was analyzed in the result section (see results section, para.3, line 3-7 and para.4, line 8-11).

2. Discussion is too heavy.

Answer: We thank the reviewer’s suggestive comments. The discussion section has been condensed accordingly (see discussion section).

Reviewer: 2

Reviewer Name: Kjell Torén

Institution and Country: Occupational and environmental medicine,Sahlgrenska University Hospital, Sweden

Please state any competing interests or state ‘None declared’: I have no competing interests to declare

Please leave your comments for the authors below

This is an interesting manuscript showing that we probably are overlooking the importance of COPD/CAL among patients with pneumoconiosis. However, to some extent the manuscript is confusing with results from methods not described in methods, but also there are some interesting results that not are presented. However, I think the manuscript has an important message.

General comments:

1. I am sceptic to use the overlap terminology, it reminds me about ACO, which is a condition that is on its way out. I would prefer to focus on the risk of COPD/CAL in relation to exposure to tobacco smoke and/or silica dust – both well known risk factors for these conditions. And probably overlooked among persons with pneumoconiosis.I am not convinced that the “overlap” condition is phenotype if itself, it is amatter of different exposure patterns. I would skip that part

Answer: Yes, we agree that the risk of COPD/CAL is in relation to exposure to tobacco smoke and/or silica dust – both well known risk factors for these conditions. The “overlap” condition is not surely convinced to be a phenotype itself. The “overlap” is skipped in the manuscript.

2. Occupational dust exposure contributes to overlapping chronic obstructive pulmonary disease and pneumoconiosis:

The definition of COPD is not clear. In the introduction is stated that COPD is CAL and symptoms (which I agree with), but later in the manuscript is the term “spirometry-defined COPD” introduced. What is that? Is it chronic airflow limitation, please be consistent regarding the used terms

Answer: We thank the reviewer’s suggestive comments. The manuscript should be consistent regarding the used terms about COPD. It has been corrected (see results section, para.2, line 5).

3. The lung function data is for me not totally clear. Here is a dynamic spirometry after bronchodilation, which is fine. But I lack which normal equations are used?I would also prefer to have the prevalence of CAL and restrictive spirometric pattern (RSP) in the different groups.

Answer: We are apologized for making the names of the two groups in Table S1 reversed. The lung function data with reversed group names induced the misunderstanding. Now the table is corrected. The prevalence of CAL (FVC/FEV1<0.70) was 100% in combined COPD and pneumoconiosis group. The prevalence of restrictive spirometric pattern (FVC<80%pred. and FVC/FEV1 0.70) was 17.2% in the group of pneumoconiosis alone.

4. TLC and RV are presented, but I cannot find that those are mentioned in the Methods. It would be of interest to get information about the prevalence of true restriction in these groups, based on the used normal values.The same with diffusion capacity.Even if they are from the hospital files, the clinical physiological laboratoryhave normal values and method descriptions.

Answer: We thank the reviewer’s comments. The normal range and method descriptions are added in methods section (see study procedure/methods section, para.2, line 13-19).

5. Bronchial challenge test is also mentioned??? Please, describe and specify.

Answer: We thank the reviewer’s suggestive comments. The cohort of patients underwent methacholine bronchial challenge test. The method are described and specified in the methods section according to your comments (see study procedure/methods section, para.2, line 6-9).

Specific comments

Abstract

In the abstract is COPD defined based on lung function. I think that is CAL.

Answer: We thank the reviewer's comments. COPD was diagnosed based on the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines. It has been corrected (see abstract section, para.4, line 5-7).

Introduction

Is coal dust an inorganic dust??

Answer: The reviewer is right. To avoid confusion, the word of "inorganic" dust is corrected (see introduction section, para. 1, line 10).

I would start the introduction with the pneumoconiosis part, and the continue with CAL/COPD. It is the pneumoconiosis population that is the base of the study.

Answer: We thank the reviewer's suggestive comments. The introduction is corrected according to the comments (see introduction section, para.1 and para. 2)

Study procedure

Reversibility of FEV1 is not airway hyperreactivity (at least not in my opinion)

Answer: Yes, the reviewer is right. The manuscript is corrected. The airway hyperreactivity is defined by a methacholine provocation concentration of 4 mg/mL or less, which led to a 20% reduction in FEV1 (PC20) (see study procedure/methods section, para. 2, line 6-9).

I think it is important to stress that emphysema and CAL are different conditions. You can have emphysema and "normal" lung function, at least not CAL. That has to be further discussed.

Answer: The reviewer is right. The emphysema and CAL are different conditions. We are apologized for making the names of the two groups in Table S1 reversed. The lung function data with reversed group names induced the misunderstanding. Now the table is corrected. As shown in Table S1, the patients with combined COPD and pneumoconiosis had significantly severe airflow limitation, increased small airway dysfunction and decreased diffusing capacity.

In Table S1 the COPD group has FEV1/FVC ranging from 74 to 81.80. Does that mean that a patient with COPD can have FEV1/FVC ratio =81.80. Please, explain that. Does it mean that the "COPD" group includes patients with emphysema and normal lung function??. That is, however, not in accordance with the initial definitions in the manuscript.

Answer: We thank the reviewer's comments. We found that we made mistakes that the names of the two groups in Table S1 were reversed. The patients with combined COPD and pneumoconiosis had FEV1/FVC ratio ranging from 24.73% to 69.91%. We now make corrections of Table S1.

My final advices:

Skip the overlap condition.

Focus on the risk for CAL associated with exposure to tobacco smoke and silica dust among patients with pneumoconiosis

Stress that we have overlooked this important aspect.

Be careful with the details in the manuscript.

Answer: We are very grateful to the reviewer's suggestive comments. The manuscript was corrected one by one according to the comments.

Reviewer: 3

Reviewer Name: Priya Paudyal

Institution and Country: Brighton and Sussex Medical School

Please state any competing interests or state 'None declared': None

Please leave your comments for the authors below

The study is well conducted and the quality of the manuscript is very good. I just have few minor comments, mainly regarding the methodology.

1. The results in the abstract could be presented in effect sizes rather than just saying the % increase.

Answer: We thank the reviewer's suggestive comments. The abstract has been corrected (see results/abstract, para.1, line11-12).

2. I am slightly confused with the study method. The method section says 'Patients with pneumoconiosis were consecutively recruited, from January 2016 to July 2019' and later says 'Clinical data were retrieved from medical records…' Did the study begin in 2016 with recruitment of participants or was it a retrospective database study based on medical records of the patients recruited between 2016-19, it needs some clarification.

Answer: We thank the reviewer's comments. The recruitment started in January 2016 and was completed in July 2019. All data were collected at the date of inclusion in the study (see settings and participants/methods, para.1, line1-3 and study procedure/methods, para.1, line2-5)

3. Also, if the sample size estimated was between 214-428, why the study included almost double number of participants?

Answer: We thank the reviewer's comments. The risk factors for COPD in pneumoconiosis were evaluated including non-smokers subgroup. The estimated sample size is 498-995 according to the proportion of non-smokers in our cohort of the patients with pneumoconiosis (see sample size/methods, para.1, line 18-21).

4. Why Mann Whitney test was used instead of T test? Was the distribution not normal?

Answer: Yes, the distribution of the data did not show normal distribution, so that Mann-Whitney U test was used instead of T test.

5. Also, in the multivariate analysis (Table 4), information should be provided on what variables were included in the model and whether the adjustments were made for these.

Answer: We thank the reviewer's comments. In the multivariate model, all variables in table 4 were included, while adjusting for age, sex, BMI and the duration of exposure and BDT (see table 4).

The findings are well discussed.

Reviewer: 4

Reviewer Name: Christian Schyllert

Institution and Country: Umeå University, Department of Public Health and Clinical Medicine, Umeå, Sweden

Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below

This paperinvestigates the clinical features of COPD among patients with pneumoconiosis. It is a very interesting study with very important results, especially for clinicians in lung medicine. I have some comments below.

1. Is the abstract accurate, balanced and complete?</i> I think the results section of the abstract can be condensed even more. For example maybe the first sentence could be in methods, to balance the sections up a little. I think the results could start with the sentence Patients with overlapping... that starts on row 31, or at least with the sentence COPD prevalence.. starting on roe 28.

Answer: We thank the reviewer’s suggestive comments. The abstract has been corrected according to comments (see setting and participants/abstract, para.1, line 2-4, and results/abstract, para.1, line 11-19).

2. Is the study design appropriate to answer the research question?</i> I believe that describing the prevalence of COPD/pneumoconiosis makes one think of a study of the general population. Maybe in the introductions last paragraph clarify that it is a population of pneumoconiosis patients. Likewise I believe that saying you want to identify risk factors of overlap also needs to be clarified that it is overlap of COPD/pneumoconiosis among pneumoconiosis patients.

Answer: Yes, the reviewer is right. The purpose of the present study was clarified to explore the risk factors for combined COPD among pneumoconiosis patients (see objectives/introduction, para.3, line13).

Reviewer: 5

Reviewer Name: Georgios Rachiotis

Institution and Country: University of Thessaly, Greece

Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below

I read with interest this well written paper which presented the results of a cross-sectional study on the prevalence and risk factors related to co-existence of pneumonoconiosis and COPD among Chinese industrial workers.

Major points

1. In the statistical analysis /methods section the authors stated that Mann Whitney test was used for the univariate analysis of continuous variables. Did the authors checked the data for normality?

Answer: We thank the reviewer’s comments. The distribution of the data was checked at first. In present study, comparisons of parametric BMI were performed by a one-way analysis of variance

(ANOVA) across four groups. Other data did not show normal distribution, so that Mann-Whitney U test was used instead of T test across two groups. The statistical analysis /methods section was modified according to your comments (see statistical analysis/methods, para.1, line 7-11).

2. I missed a statement in statistical analysis/methods section regarding the methdology used for the assessment of the possible interaction between smoking and work-related chemical hazards.

Answer: Yes, the reviewer is right. The statement in statistical analysis regarding the methodology used for the assessment of the possible interaction between smoking and work-related chemical hazards is added according to the comments(see statistical analysis/methods section, para.1, line17-19).

3. In the last sentence of the manuscript the authors concluded that they found:" high risk of occupational dust exposure for COPD and pneumoconiosis overlap and calls for urgent preventive intervention". They may further discuss this issue and they could mention examples of "urgent preventive intervemtions" (e.g. combined control of smoking and occupational exposures).

Answer: We thank the reviewer's suggestive comments. The preventive interventions are further discussed for reducing the possible risks of combined COPD and pneumoconiosis (see conclusion section, para.1, line14-19) .

VERSION 2 – REVIEW

REVIEWER	Satoshi Hamada Country: Japan Institution: Kyoto University
REVIEW RETURNED	18-Jul-2020

GENERAL COMMENTS	1. Pneumoconiosis is the disease with restrictive ventilatory defect, whereas COPD is the disease with obstructive ventilatory defect. Therefore, in peumoconiosis, COPD could be underestimated. 2. Authors should describe the data of pulmonary function tests. 3. This manuscript is too long. 4. Please recheck the reference stile.

REVIEWER	Kjell Torén Occupational and Environmental Medicine/School of Public health and Community Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden
REVIEW RETURNED	08-Jul-2020

GENERAL COMMENTS	The authors have revised the manuscript adequately, and I have no further comments

REVIEWER	Priya Paudyal Brighton and Sussex Medical School, UK
REVIEW RETURNED	09-Jul-2020

GENERAL COMMENTS	The author's have addressed the concerns I raised earlier, I am happy for this article to be published.

REVIEWER	Christian Schyllert Public Health and Clinical Medicine, Umeå University, Umeå, Sweden
REVIEW RETURNED	06-Jul-2020

GENERAL COMMENTS	The manuscript has improved and previous comments have been adressed appropriately.

REVIEWER	Georgios Rachiotis University of Thessaly, GREECE
REVIEW RETURNED	18-Jul-2020

GENERAL COMMENTS	The authors have adequately addressed all my comments.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name
Satoshi Hamada
Institution and Country
Country: Japan
Institution: Kyoto University
Please state any competing interests or state ‘None declared’:
None
Please leave your comments for the authors below

1. Pneumoconiosis is the disease with restrictive ventilatory defect, whereas COPD is the disease with obstructive ventilatory defect. Therefore, in pneumoconiosis, COPD could be underestimated.

Answer: Yes, it is possible that COPD may be underestimated in the patients with some of the pneumoconiosis such as asbestosis. We make further discussion (see section discussion, para.3, line 10-14).

2. Authors should describe the data of pulmonary function tests.

Answer: We thank the reviewer’s suggestive comments. Lung function impairment in all pneumoconiosis was a mild obstructive ventilatory defect combined with the small airway dysfunction (see Table S1). Among which the lung function impairment in the asbestosis was a mild mixed ventilatory defect with diffusion dysfunction and small airway dysfunction as well (see Supplementary table). The patients with combined COPD and pneumoconiosis also differed from those with pneumoconiosis alone in a range of lung function measures (Table S1). In particular, compared with those without COPD, patients with COPD had significantly more severe airflow limitation, increased small airway dysfunction and decreased membrane diffusing capacity (see results section, para.3, line 4-8).

Supplementary table Pulmonary function tests of the patients with pneumoconiosis

Variables	Asbestosis	Silicosis	Coal workers' pneumoconiosis	Other pneumoconiosis	p-value
n	130	210	259	76	
FVC, %pred	82.80 (67.28-98.18)	100.30 (85.30-110.25)	100.50 (87.00-111.00)	87.55 (99.3-112.05)	<0.001
FEV_1, %pred	81.20 (65.40-96.20)	88.25 (71.70-100.88)	91.40 (72.70-104.60)	93.70 (81.28-105.72)	0.001
FEV_1/FVC, %	78.70 (72.24-82.72)	72.60 (63.71-78.65)	72.83 (64.83-78.42)	76.60 (70.78-80.76)	<0.001
DLco SB, %pred	72.00 (58.50-88.20)	85.50 (66.65-95.88)	90.40 (76.10-104.80)	91.30 (77.55-104.25)	<0.001
TLC, %pred	75.40 (65.00-84.00)	95.80 (84.03-103.28)	96.40 (87.30-106.60)	95.15 (85.80-105.50)	<0.001
RV, %pred	80.90 (65.60-95.00)	102.45 (88.43-122.05)	111.70(95.60-137.70)	104.20 (88.35-117.85)	<0.001
RV/TLC, %	44.21 (38.49-52.26)	39.23 (35.27-47.80)	39.56 (34.29-47.00)	35.90 (29.01-45.52)	<0.001
PEF, %pred	95.50 (74.50-114.40)	91.35 (69.57-106.43)	90.90 (74.40-106.50)	102.15 (85.35-119.62)	0.002
MEF_{75}, %pred	81.10 (58.90-117.20)	73.50 (47.43-98.20)	77.30 (49.40-100.20)	95.55 (70.90-119.50)	<0.001
MEF_{50}, %pred	54.60 (38.30-82.20)	52.75 (35.53-73.78)	60.70 (39.00-79.00)	72.75 (54.83-93.93)	0.001
MEF_{25}, %pred	44.10 (30.00-68.50)	41.90 (27.93-58.25)	48.30 (31.00-63.80)	48.15 (37.65-65.93)	0.050

Values were given as the median (IQR).

Abbreviations: FVC: forced vital capacity; FEV_1: forced expired volume in the first second; DLco SB: diffusion capacity for carbon monoxide of the lung single breath; TLC: total lung capacity; RV: residual volume; PEF: peak expiratory flow; MEF_{25}: maximal expiratory flow after 25% of the FVC has been not exhaled. MEF_{50}: maximal expiratory flow after 50% of the FVC has been not exhaled; MEF_{75}: maximal expiratory flow after 75% of the FVC has been not exhaled; IQR: interquartile range

3. This manuscript is too long.

Answer: We thank the reviewer's suggestive comments. We recheck the manuscript according to your comments. Now the word counts of the manuscript are 3,275 words which are shorter than the required article lengths of the journal (not exceed 4000 words).

4. Please recheck the reference stile.

Answer: We thank the reviewer's comments. We recheck the reference stile.

Reviewer: 2

Reviewer Name

Kjell Torén

Institution and Country

Occupational and Environmental Medicine/School of Public health and Community Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

Please state any competing interests or state 'None declared':

None declared

Please leave your comments for the authors below

The authors have revised the manuscript adequately, and I have no further comments

Reviewer: 3

Reviewer Name

Priya Paudyal

Institution and Country

Brighton and Sussex Medical School, UK

Please state any competing interests or state 'None declared':

None

Please leave your comments for the authors below

The author's have addressed the concerns I raised earlier, I am happy for this article to be published.

Reviewer: 4
Reviewer Name
Christian Schyllert
Institution and Country
Public Health and Clinical Medicine, Umeå University, Umeå, Sweden
Please state any competing interests or state ‘None declared’:
None declared
Please leave your comments for the authors below
The manuscript has improved and previous comments have been adressed appropriately.

Reviewer: 5
Reviewer Name
Georgios Rachiotis
Institution and Country
University of Thessaly, GREECE
Please state any competing interests or state ‘None declared’:
None declared.
Please leave your comments for the authors below
The authors have adequately addressed all my comments.